Tamoxifen for retroperitoneal fibrosis

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Summary

Retroperitoneal fibrosis, either idiopathic or associated with aortic inflammatory aneurysm, is a chronic fibrotic disease that causes progressive obstruction of ureters and vessels around the lower abdominal aorta. Treatment is often difficult (surgery) or hazardous (steroids). We report a case of a woman with retroperitoneal fibrosis associated with aortic inflammatory aneurysm, who was successfully treated with oral tamoxifen.

Keywords: tamoxifen, retroperitoneal fibrosis

Retroperitoneal fibrosis, sometimes associated with aortic inflammatory aneurysm, is a rare but serious fibrotic process that surrounds the lower abdominal aorta and causes progressive obstruction of one or both ureters and the inferior vena cava leading to impaired renal function and lower limb oedema.[1] Surgical ureterolysis and aneurysm resection are classical treatments but remain hazardous and are frequently complicated. Alternatively, steroid therapy, previously reported by Baskerville *et al* in 1983[2] and Leseche in 1992,[3] is often acutely beneficial but may promote aneurysmal rupture and result in major side-effects because of long duration treatment.[3] A successful response with tamoxifen has been reported in a few cases of idiopathic disease[4,5] but, to our knowledge, has not been used in retroperitoneal fibrosis associated with aortic inflammatory aneurysm.

Case report

A 63-year-old woman with a history of smoking and inferior myocardial infarction, presented with chronic lumbar pain for some weeks. There were no urinary tract symptoms nor changes in bowel habits. Clinical examination was normal. Blood laboratory tests showed a erythrocyte sedimentation rate (ESR) of 65 mm/h, urea nitrogen at 17.8 mmol/l (normal 2.5–6.4) and creatinine at 220 μmol/l (normal 53–97). There was a slight hypergammaglobulinaemia. Tumour markers were negative. Urine was sterile. Computed tomography (CT) scan revealed retroperitoneal fibrosis surrounding a partially calcified infrarenal aortic aneurysm with bilateral ureterohydronephrosis (figure 1) compatible with aortic inflammatory aneurysm. Tamoxifen 10 mg bid was started. CT scan after two months of treatment showed a partial resolution of left hydronephrosis. However, because renal impairment persisted, bilateral ureteral double-J stents were inserted. Subsequently, two months later, CT scan revealed disappearance of the hydronephrosis and a dramatic regression of retroperitoneal fibrosis. Blood urea nitrogen was 14.3 mmol/l and creatinine was 167 μmol/l. The double-J catheters were removed. More than two years after this therapy, renal function remains stable (urea: 9.6 mmol/l; creatinine: 141 μmol/l), ESR is normalised at 17 mm/h and CT scan does not show any recurrence of retroperitoneal fibrosis nor aggravation of aortic aneurysm (figure 2). No side-effects of tamoxifen were noted apart from hepatic steatosis, revealed by ultrasonography and CT scan (figure 2) and associated with a moderate increase in plasma γ-glutamyltransferase (64 *vs* 42 U/l before treatment; normal ⩽30).

Discussion

Several aetiologic factors associated with retroperitoneal fibrosis have been recognised, such as long-term use of ergot derivates, metastatic foci of adenocarcinomas, lymphomas and

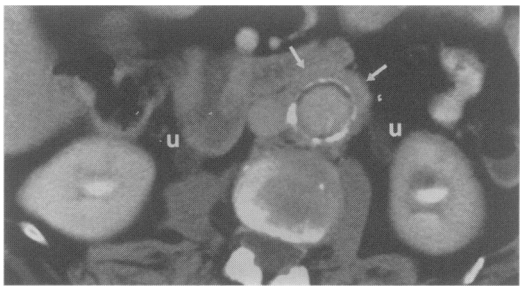

Figure 1 Initial enhanced CT scan. Retroperitoneal fibrosis is indicated by arrows (aortic aneurysm diameter: 30 × 22 mm). u: ureters

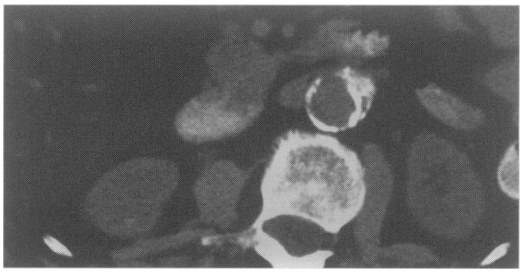

Figure 2 Unenhanced CT scan after treatment. Ureterohydronephrosis and retroperitoneal fibrosis have disappeared. The difference of level with figure 1 does not exceed 5 mm

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retroperitoneal haemorrhages. However, many cases are idiopathic or associated with aortic aneurysm, an entity sometimes named chronic peri-aortitis.[1] It has been postulated that this peri-aortic fibrosis is an immune response to the leakage of insoluble lipids (ceroids) from atheroslerotic plaques. The term 'inflammatory aortic aneurysm' was introduced in 1972 by Walker *et al* who described it as an excessive thickening of the wall of the abdominal aorta surrounded by retroperitoneal fibrosis involving the adjacent structures.[6] Abdominal aortic dilatation in our patient was small but corresponded to the definition of aneurysm (external aortic diameter >2 cm) as previously reported.[7] Ureteral obstruction was present in our patient, a feature also previously described by Schloss and Kaplan in 1953.[8]

In view of her previous myocardial infarct and the small size of the aneurysm, we chose nonoperative management. The anti-oestrogen tamoxifen, commonly used for breast carcinoma treatment, is also active on desmoid tumours, a benign fibrotic process. This drug was first used in two patients with idiopathic retroperitoneal fibrosis by Clark *et al*[4] and its use has since been reported in another patient.[5]

As spontaneous regression of retroperitoneal fibrosis is very rare,[9] it appears that tamoxifen is responsible for this beneficial effect. Its mechanism of action is not entirely understood.[4] The induction of transforming growth factor beta in stromal fibroblasts by tamoxifen has recently been advocated.[10] Unlike steroids, this favourable response is slow in onset. In the present case or those reported in the literature,[4,5] ureteral stents associated with tamoxifen might have accelerated the regression of retroperitoneal fibrosis and the improvement of renal function. However, it must be stressed that, in our case, left hydronephrosis regressed before stent introduction and retroperitoneal fibrosis did not recur after stent removal. Moreover, complete remission after placement of a ureteral stent only is unlikely. As retroperitoneal fibrosis could relapse after tamoxifen discontinuation,[4] we preferred to keep our patient on this medication. Long-term tolerance of tamoxifen is generally excellent although rare cases of steatohepatitis have been described.[11] In our case, only a mild steatosis was noted.

Thus, clinicians should be aware that tamoxifen is an alternative and comparatively safe therapy of idiopathic inflammatory aneurysm associated with retroperitoneal fibrosis.

Retroperitoneal fibrosis

- *pathology:* chronic inflammatory fibrotic tissue around lower abdominal aorta that causes obstruction of ureters and inferior vena cava
- *aetiology:* ergot derivates (ergotamine, methysergide, bromocriptine, etc), idiopathic, inflammatory aortic aneurysm, malignancies (metastatic adenocarcinomas, lymphomas), retroperitoneal haemorrhage (spontaneous or postsurgical)
- *clinical findings:* nonspecific (fatigue, low back or abdominal pain, weight loss, anaemia, elevated ESR) and specific (hydronephrosis, renal failure, peripheral oedema, deep thrombophlebitis)
- *diagnosis:* CT scan (or MRI)
- *treatments:* surgical ureterolysis, aneurysmal resection, ureteral stents, steroids ($\pm$azathioprine), tamoxifen

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